

WE CLAIM:

1. A method for treating a condition associated with the excess accumulation of extracellular matrix in a tissue and/or organ or at a dermal wound site comprising:

5 a) reducing the excess accumulation of extracellular matrix associated with TGF β overproduction and/or activity in an organ or tissue, or at a wound site; and

10 b) degrading excess accumulated extracellular matrix in said tissue and/or organ or wound site;

whereby the accumulation of extracellular matrix in said tissue and/or organ or wound site is reduced from the level existing at the time of treatment.

15 2. The method of claim 1 wherein the accumulation of extracellular matrix is reduced to a level which does not interfere with normal functioning of the tissue or organ or result in scarring.

20 3. The method of claim 1 wherein said step of reducing the accumulation of extracellular matrix comprises administering at least one agent that inhibits TGF β in an amount sufficient to inhibit TGF β overproduction and/or activity.

25 4. The method of claim 3, wherein said agent that inhibits TGF β is selected from the group consisting of selected from the group consisting of inhibitors of aldosterone, inhibitors of angiotensin II, anti-TGF β antibodies, renin, ACE inhibitors, AII receptor antagonists, proteoglycans and ligands for the TGF β receptor.

5. The method of claim 4 wherein said agent is a proteoglycan selected from the group consisting of decorin, biglycan, fibromodulin, lumican, betaglycan and endoglin.

30 6. The method of claim 4 wherein said ACE inhibitor is Enalapriltm.

7. The method of claim 4 wherein said AII receptor antagonist is Losartantm.

8. The method of claim 1 wherein said step of reducing the accumulation of extracellular matrix associated with TGF β activity comprises contacting renin with an anti-renin agent.

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9. The method of claim 1 wherein said step of degrading excess accumulated extracellular matrix comprises contacting said matrix with at least one protease in an amount sufficient to degrade excess accumulated extracellular matrix to a level that does not impair the normal function of said tissue and/or organ or result in scarring.

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10. The method of claim 9 wherein said protease is selected from the group consisting of serine proteases, metalloproteinases and protease combinations.

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11. The method of claim 1 wherein said step of degrading accumulated extracellular matrix comprises administering an agent which increases the amount of active protease sufficient to degrade excess accumulated matrix to a level that does not impair the normal function of said tissue and/or organ or result in scarring.

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12. The method of claim 11 wherein said protease is selected from the group consisting of serine proteases, metalloproteinases and protease combinations.

13. The method of claim 12 wherein said protease is plasmin and said agent which increases the amount of active plasmin is tPA.

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14. The method of claim 12 wherein said protease is plasmin and said agent which increases the amount of active plasmin is a PAI-1 mutant.

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15. The method of claim 1 wherein said condition associated with the excess accumulation of extracellular matrix is a fibrotic condition.

16. The method of claim 15 wherein said fibrotic condition is selected from the group consisting of glomerulonephritis, adult or acute respiratory distress syndrome (ARDS), diabetes, diabetic kidney disease, liver fibrosis, kidney fibrosis, lung fibrosis, post infarction cardiac fibrosis, fibrocystic diseases, fibrotic cancer, post myocardial infarction, left ventricular hypertrophy, pulmonary fibrosis, liver cirrhosis, veno-occlusive disease, post-spinal cord injury, post-retinal and glaucoma surgery, post-angioplasty restenosis, renal interstitial fibrosis, arteriovenous graft failure and scarring.

17. The method of claim 1 wherein said tissue or organ is selected from the group consisting of kidney, lung, liver, heart, arteries, skin and the central nervous system.

18. The method of claim 1 wherein said condition associated with the excess accumulation of extracellular matrix is scarring.

19. The method of claim 3 wherein said agent that inhibits $TGF\beta$ is nucleic acid encoding the agent.

20. The method of claim 9 wherein said protease is nucleic acid encoding a protease.

21. A method for treating a condition associated with the excess accumulation of extracellular matrix in a tissue and/or organ or at a wound site comprising:

a) administering at least one agent that inhibits $TGF\beta$ to reduce additional accumulation of extracellular matrix associated with $TGF\beta$ activity in a tissue and/or organ or at a wound site; and

b) administering at least one agent to degrade excess accumulated extracellular matrix; whereby the accumulation of extracellular matrix in said tissue and/or organ or at said wound site is reduced to a level which does not interfere with normal functioning of the tissue or organ in which said extracellular matrix accumulated.

22. The method of claim 21 wherein said agent that inhibits TGF β and said agent to degrade excess accumulated extracellular matrix are administered concurrently.

23. The method of claim 21 wherein said agent that inhibits TGF β and said agent to degrade excess accumulated extracellular matrix are administered sequentially.

24. The method of claim 21 wherein the agent that inhibits TGF β is an anti-TGF β specific agent that binds to and inhibits the activity of TGF β .

25. The method of claim 21 wherein the agent that inhibits TGF β is an agent selected from the group consisting of inhibitors of aldosterone, inhibitors of angiotensin II, anti-TGF β antibodies, renin, ACE inhibitors, AII receptor antagonists, proteoglycans and ligands for the TGF β receptor.

26. A method for treating or preventing a condition associated with the excess accumulation of extracellular matrix in a tissue and/or organ, or at a wound site, comprising administering a combination of agents in an amount sufficient to inhibit TGF β activity and/or production to prevent or reduce the excess accumulation of extracellular matrix associated with TGF β overproduction in a tissue and/or organ, or at a wound site.

27. The method of claim 26 wherein the agents to inhibit TGF β comprise an agent that binds to and inhibits the activity of TGF β and an agent selected from the group consisting of inhibitors of aldosterone, inhibitors of angiotensin II, inhibitors of renin, ACE inhibitors and AII receptor antagonists.

28. The method of claim 27 wherein said agent that binds to and inhibits the activity of TGF β is selected from the group consisting of anti-TGF β antibodies, proteoglycans and ligands for the TGF β receptor.

29. The method of claim 28 wherein said agent that binds to and inhibits the activity of TGF β is a proteoglycan selected from the group consisting of decorin, biglycan, fibromodulin, lumican, betaglycan and endoglin.

30. The method of claim 26 wherein said agents are nucleic acids encoding said respective agents.

5 31. The method of claim 26 wherein said agents are administered to reduce TGF β overproduction prior to excess accumulation of extracellular matrix.

32. A method for preventing or reducing excess extracellular matrix accumulation in a tissue or organ or at a wound site comprising inhibiting the overproduction of TGF β present in an organ
10 or tissue or at a wound site to prevent

33. The method of claim 32 further comprising the step of degrading excess accumulated extracellular matrix in said tissue and/or organ or at said wound site.

15 34. The method of claim 32 wherein said accumulation of extracellular matrix is reduced to a level which does not interfere with the normal functioning of the tissue and/or organ in which said extracellular matrix accumulated or scarring is prevented or reduced.

20 35. A composition for reducing TGF β overproduction in a tissue and/or organ or at a wound site comprising a combination of agents that inhibit TGF β activity and/or production in a pharmaceutically acceptable carrier.

36. The composition of claim 35 wherein said agents comprise an agent that binds to and inhibits TGF β and an agent that inhibits a pathway resulting in TGF β production.

25 37. A composition for preventing or reducing excess accumulation of extracellular matrix associated with TGF β activity comprising at least one agent that inhibits TGF β activity and/or production and at least one agent that degrades excess accumulated extracellular matrix in a pharmaceutically acceptable carrier.

38. The composition of claim 37 wherein said agent that inhibits TGF β is an agent that binds to and inhibits TGF β , and said agent that degrades excess accumulated extracellular matrix is a protease.

5 39. The composition of claim 38 wherein said agent that inhibits TGF β is selected from the group consisting of inhibitors of aldosterone, inhibitors of Angiotensin II, anti-TGF β antibodies, renin, ACE inhibitors, AII receptor antagonists, proteoglycans and ligands for the TGF β receptor.

10 40. The composition of claim 38 wherein said protease is selected from the group consisting of serine proteases, metalloproteinases and protease combinations.

41. The composition of claim 39 wherein said proteoglycan is selected from the group consisting of decorin, biglycan, fibromodulin, lumican, betaglycan and endoglin.

15 42. The composition of claim 37 wherein said agent that inhibits TGF β and said agent that degrades excess accumulated extracellular matrix are nucleic acids encoding said agents respectively.

20 43. The composition of claim 37 wherein said agent that degrades excess accumulated extracellular matrix is an agent that increases the amount of active protease present in the tissue and/or organ or at a wound site.

44. The composition of claim 43 wherein said protease is plasmin and said agent is tPA.

25 45. The composition of claim 43 wherein said protease is plasmin and said agent is a PAI-1 mutant.

30 46. A composition for reducing the excess accumulation of extracellular matrix in a tissue and/or organ, or at a dermal wound site, comprising an agent that increases the amount of active protease present in the tissue and/or organ or at the wound site in a pharmaceutically acceptable carrier.

47. The composition of claim 46 wherein said protease is plasmin and said agent is tPA.

48. The composition of claim 46 wherein said protease is plasmin and said agent is a PAI-1 mutant.

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49. A composition for treating a condition associated with the excess accumulation of extracellular matrix in a tissue and/or organ or at a dermal wound site comprising a combination of agents that inhibit TGF β in a pharmaceutically acceptable carrier.

10 50. The composition of claim 49 wherein said agents that inhibit TGF β are selected from the group consisting of inhibitors of aldosterone, inhibitors of inhibitors of aldosterone, inhibitors of angiotensin II, anti-TGF β antibodies, renin, ACE inhibitors, AII receptor antagonists, proteoglycans and ligands for the TGF β receptor.

15 51. The composition of claim 50 wherein said proteoglycans are selected from the group consisting of decorin, biglycan, fibromodulin, lumican, betaglycan and endoglin.